Review article

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Outcome after epilepsy surgery in children with MRI-negative non-idiopathic focal epilepsies

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ABSTRACT – MRI is one of the most important diagnostic tools in the presurgical evaluation of patients suffering from pharmaco-refractory focal epilepsies. Presence of a lesion on MRI influences both diagnostic classification as well as selection for surgery; however, the implications for MRI-negative cases are far from well defined for such patients. Detection of potentially epileptogenic lesions depends on the techniques applied (high-field MRI, post-processing, etc.) and the experience of the neuroradiologist. The proportion of MRI-negative patients in reported epilepsy surgery cohorts ranges from 16 to 47%. Most MRI-negative patients undergo invasive long-term EEG recordings before a final decision regarding resection is possible. Post-operative seizure freedom rates, with few exceptions, range from 40 to 50%. Selection of surgical candidates and post-operative outcomes may be improved by recent developments in structural and functional imaging techniques and multimodal approaches. This report gives an overview of outcomes after epilepsy surgery in MR-negative patients with a focus on children. Issues regarding definitions, the role of established and recently introduced diagnostic tools, and the question of how outcome might be improved in the future are discussed.

Key words: epilepsy surgery, childhood, outcome, cryptogenic, MRI, functional imaging

During the presurgical evaluation for epilepsy, the most challenging aspects regarding the identification of an epileptogenic zone are represented by two scenarios: too many and/or widespread diffuse lesions (*i.e.* tuberous sclerosis complex, hemispheric or multilobar lesions in patients without neurological impairment) and, conversely, no lesion at all, or only non-specific changes, identified by structural imaging. Without a doubt, MRI is one of the most important diagnostic tools in presurgical evaluation. The proportion of MRI-negative (MR-) patients referred for presurgical work-up varies between 16% (Bien *et al*., 2009) and 32% (Berg *et al*., 2003). A survey by the ILAE Pediatric Epilepsy Surgery Survey Taskforce revealed that MRI scans were

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obtained in 99.5% of all operated children (Harvey *et al*., 2008). MRI was reported to show a clear lesion in 77% of cases and a subtle or suspected lesion in 6%. A total of 17% of children were MRI-negative.

The proportion of MRI-negative patients within published surgical cohorts varies between 18 and 47% (Scott *et al*., 1999; Paolicchi *et al*., 2000; Siegel *et al*., 2001; Berg *et al*., 2003; McGonigal *et al*., 2007; Bien *et al*., 2009; Téllez-Zenteno *et al*., 2010). A meta-analysis demonstrated a significantly higher proportion of MRI-negative cases in children, compared to adults (31 *vs* 21%, respectively), and patients with extratemporal lobe epilepsy (ETLE) (Téllez-Zenteno *et al*., 2010).

Thus far, there is no comprehensive and generally accepted concept of how MRI-negative children and adults with pharmaco-refractory focal epilepsies should be selected for presurgical evaluation, and which diagnostic tools should be used to identify candidates for the respective modes of epilepsy surgery. Most studies on postsurgical outcome in MRI-negative patients have included mainly adults and few data have been reported for exclusively paediatric cohorts (Paolicchi *et al*., 2000; RamachandranNair *et al*., 2007; Jayakar *et al*., 2008; Dorward *et al*., 2011; Seo *et al*., 2011). Age-dependent differences are expected since widespread and extratemporal epileptogenesis related to developmentally malformed cortex is more common in children (Jayakar *et al*., 2008).

Differentiation between monofocal and truly multifocal seizure origins may be complicated in young children. A major reason may be the inconclusive presentation, including an apparently generalised aspect of EEG patterns and seizure semiology, in very young children. Jayakar *et al*. (2008) stated "*selection of surgical candidates varies between centres depending on the availability of collective expertise and experience in clinical, neurophysiological, and functional imaging interpretation*".

Based on two reports, the proportion of patients who receive surgery following presurgical evaluation significantly correlates with the presence or absence of an MRI lesion; 81 *vs* 45% (Berg *et al*., 2003) and 73 *vs* 15% (Bien *et al*., 2009), respectively. The decision to perform resective surgery following invasive EEG (iEEG) recording is more often made in MRI-positive (MR+) cases; 91% of patients with MR+ *vs* 54% in MRI-negative patients (Alarcón *et al*., 2006).

Definitions and the role of MRI

The terms "*cryptogenic*" or "*non-lesional*" have been widely used to characterise patients with epilepsy of unknown cause. However, these terms are imprecise because the methods leading to the categorisation remain unclear. "*Non-lesional*" may be attributed to MRI-negative patients, as well as to those with negative histopathology (Bien *et al*., 2009; Téllez-Zenteno *et al*., 2010). A negative MRI does not automatically mean that the aetiology will remain unclear after resection. About one to two thirds of all resective specimens of MRI-negative patients show specific pathological lesions that are commonly related to epileptogenicity (Cukiert *et al*., 2001; Siegel *et al*., 2001; Hong *et al*., 2002; Sylaja *et al*., 2004; Chapman *et al*., 2005; Lee *et al*., 2005; Alarcón *et al*., 2006; McGonigal *et al*., 2007; Bell *et al*., 2009; Bien *et al*., 2009). Methods of imaging have failed to detect the underlying structural cause of epilepsy in these cases.

Most studies reported focal cortical dysplasia (FCD) as the most frequent identifiable aetiology in MRI-negative ETLE (Cukiert *et al*., 2001; Chapman *et al*., 2005; Lee *et al*., 2005; RamachandranNair *et al*., 2007; Bien *et al*., 2009; Brodbeck *et al*., 2010; Seo *et al*., 2011; Wu *et al*., 2013). Because pathology is available only after resection, the term "*non-lesional*" is impractical, regarding the decision to operate. During evaluation, structural MRI is the gold standard to identify clear candidates for epilepsy surgery. Complicated cases requiring extensive and multimodal work-up are exempt from this group. The term "*MRI negative*" is used here to characterise this challenging subgroup of focal epilepsies.

However, the definition of "*MRI-negative*" is controversial. The number of positive findings depends on the techniques used, and data should be confirmed, reported, and eventually analysed collectively. In addition, the experience of the reviewer plays a vital role which cannot easily be controlled or compared. This applies particularly to studies with new diagnostic methods. Compared to the 1990s, MRI is currently under rapid development with the introduction of high-field 3T MRI in routine clinical practice and the application of new methods (diffusion tensor imaging (DTI), voxel-based post-processing, etc.). Presumably, patients previously classified as MRI-negative may actually be MR+. Therefore, a comparison between previous and current MRI-negative patients may be inaccurate or even impossible.

The challenge associated with MRI- cases was highlighted in a study by the Epilepsy Center in Bonn (von Oertzen *et al*., 2002). Non-experts reported lesions on routine MRI in only 39% of patients with a histopathological substrate. When the same routine MRI scans were reviewed by experts, the proportion of MR+ cases increased by 50%. High-resolution MRI to specifically detect lesions associated with epilepsy demonstrated a sensitivity of 91%. An MRI lesion was detected in 85% of standard MRI-negative patients. Based on *post-hoc* analysis, the number of MR+ patients increased, relative to presurgical evaluation, if the reviewer was aware of the underlying pathological substrate. With

this knowledge of pathological substrate, Bien *et al*. (2009) further carefully re-analysed MRI after surgery revealing an underlying lesion in 8 of 9 patients who were previously MRI-negative.

Although 3T MRI has become the standard in the presurgical evaluation of epilepsy, few data exist on its potential superiority over 1.5T to identify candidates. The most important advantage would be an improvement in surgical outcome; however, this has yet to be demonstrated. Knake *et al*. (2005) applied 3T phase array MRI in 23 patients with previously negative 1.5T MRI and found lesions in 15 (65%). One significant shortcoming was that 1.5T MRI was analysed only by radiologists at the referring centres and not by a central and blinded reviewer. In addition, effects from phase array and 3T field techniques could not be differentiated. Other studies reported lower rates (5.6 to 20%) of newly detected lesions on 3T MRI (Strandberg *et al*., 2008; Nguyen *et al*., 2010). Interestingly, 3T is not necessarily superior (Zijlmans *et al*., 2009). Two experienced blinded neuroradiologists re-evaluated 1.5T and 3T MRI with phased-array coils of 37 patients, considered ineligible for surgery. One found 22 lesions in both 1.5T and 3T, and surprisingly, the other detected more lesions in 1.5T (28 *vs* 20 in 3T). The use of post-processing methods may increase the number of MR+ patients during presurgical evaluation. Lesions may be detected independently of the reviewer's experience using voxel-based morphometric post-processing of 3D-T1 data (Huppertz *et al*., 2005). This method was compared with visual evaluation in 91 patients with defined FCD type 2 (FCD2a 17, FCD2b 74) (Wagner *et al*., 2011). Whereas a similar high proportion of FCD2b was detected (92 *vs* 91%) using both approaches, morphometric analysis was superior in detecting FCD2a (82 *vs* 65%). Most importantly, the combination of morphometry and visual inspection was significantly more sensitive, compared to visual evaluation alone (98 *vs* 86%). Voxel-based analysis based on 3T FLAIR may lead to even higher rates of FCD detection (Riney *et al*., 2012). FLAIR morphometry was correct in 7/8 cases compared to 3/8 for T1. DTI has been shown to provide additional information in patients with MRI-negative ETLE in a multimodal diagnostic setting (Thivard *et al*., 2011). It is difficult to detect discrete malformations in infants under the age of 2 because of their immature myelination. Before 6 months of age, MRI may detect FCD with a typically low T2 signal. Thereafter, lesions may become less apparent or even disappear during maturation before myelination is complete (Duprez *et al*., 1998; Eltze *et al*., 2005). MRI negativity under 2 years of age requires repeat MRI in later life.

Abnormalities may be detected using advanced techniques in about 50% of patients with previously negative MRI (Koepp and Woermann, 2005). However, these abnormalities do not necessarily correlate with the epileptogenic zone, as revealed by functional methods. Increasing sensitivity of imaging methods may unintentionally increase the number of innocuous lesions. At best, these lesions confuse the neurologist. At worst, the placement of invasive electrodes or even resections may be incorrect. Thus, interpretation of structural imaging requires a context of clinical findings and information from functional studies.

Seizure outcome after surgery for MRI-negative focal epilepsy

Many studies have reported post-operative outcome in MRI-negative cohorts of adults and children (*table 1*). Some studies were intended to demonstrate the clinical value of new diagnostic methods. Only few studies have exclusively focused on children and adolescents.

The largest group of 102 MRI-negative children and adolescents who received surgery (93 patients less than 18 years; age: 0.5 to 21 years; mean: 10.7 years) was reported by the Miami group (Jayakar *et al*., 2008). Of the 102 patients, 80 underwent extra-operative long-term iEEG recording. Seizure freedom rates after 2, 5, and 10 years were 44, 44, and 38%, respectively, and a reduction in seizure frequency of at least 90% was achieved in 58, 59, and 68%, respectively. Dorward *et al*. (2011) investigated 33 children who underwent surgery for MR- ETLE. Procedures included resections and multiple subpial transections (MST). Engel class I outcome was achieved in 42.4%. Seven of 14 MRI-negative children, who underwent multimodal functional imaging and resections between 2006 and 2009, became seizure-free (Seo *et al*., 2011). During this period, a total of 25 MRI-negative children received surgery at this centre and 12 (48%) were rendered seizure-free. RamachandranNair *et al*. (2007) investigated the impact of magnetoencephalography (MEG) and iEEG on surgery in 22 MRI-negative children. Eight (36%) became seizure-free and 17 (77%) had at least an Engel class IIIa outcome.

A recent review and meta-analysis compared surgical outcome for lesional and non-lesional epilepsy (Téllez-Zenteno *et al*., 2010). Ninety-two articles published from 1995 to 2007 were summarised and 40 were used for the meta-analysis. The analysis involved a comparison of results from 697 patients with non-lesional epilepsy and 2,860 patients with lesional epilepsy. Absence of a lesion was a clear negative predictor regarding seizure freedom, there were no significant differences between children and adults, and the fact that a non-lesional status was based on MRI or histopathology was not significant. The rate of seizure freedom for MRI-negative patients

was 46% (95% CI: 39-46), compared to 70% (95% CI: 68-73) for MR+ patients. The odds ratio for seizure-free outcome in MR+ patients was 2.4 (95% CI: 1.8-3.2). For ETLE, a seizure-free outcome was achieved in 60% (54-66) of MR+ patients, compared to 35% (27-42) of MRI-negative patients. The results from children were not significantly different. In children, only results for non-lesional cases, with a classification based on either MRI or histopathology, were reported. The seizure freedom rate was 45% (35-55) in 93 children without a lesion, compared to 74% (69-79) in 317 lesional cases.

A methodological shortcoming of this meta-analysis is the inability to separate contributory factors, such as type of MRI, results of invasive recordings and functional imaging, type of surgery, and many others. Only one study included in the review exclusively reported on children (Paolicchi *et al.,* 2000). The study included 75 of 83 children who received surgery under the age of 12. All 35 MRI-negative and 20 of 40 MR+ cases underwent iEEG with subdural electrodes. The high proportion of MRI-negative patients may be specifically attributed to the centre in Miami, with corresponding referrals. A large proportion of children was only investigated using 0.5T MRI. A total of 59% became seizure-free after surgery without significant difference between 35 MRI-negative and 40 MR+ cases (56 *vs* 70%, respectively). A reduction of seizure frequency of >90% was observed in 80% of MR+ and 67% of MRI-negative children.

The lack of an MRI lesion led to a significantly lower seizure freedom rate (38 *vs* 66% in MR+ cases) in 29 MRI-negative and 736 MR+ patients operated upon at the Epilepsy Center in Bonn (Bien *et al*., 2009). While 7/9 MRI-negative patients with confirmed histopathological lesions became seizure-free, only 4/20 with normal or non-specific pathology became seizure-free. McGonigal *et al*. (2007) reported outcome in 60 patients who received surgery after evaluation by stereo-EEG. Seizure freedom rates did not differ between the MRI-negative and MR+ groups (MR-: 11/20 [55%]; MR+: 21/40 [53%]). In the context of a MEG study, Zhang *et al*. (2011) reported 20 MRI-negative and 23 MR+ patients who received surgery; the seizure freedom rate was significantly lower in MRI-negative patients (35%), compared to MR+ cases (65.2%).

The outcome after surgery for MRI-negative frontal lobe epilepsy is inconclusive. While some studies reported a worse outcome compared to MR+ cases (Jeha *et al*., 2007; Elsharkawy *et al*., 2008), a recent study found no differences in seizure control between MRI-negative (15/26 [58%] seizure-free) and MR+ (17/32 [53%] seizure-free) cases (Lazow *et al*., 2012).

In summary, a difference in seizure-free outcome between MRI-negative and MR+ cases following epilepsy surgery was identified in some studies, but not all. It is well known that the extent of resection influences outcome. Completeness of resection of the underlying lesion is the most consistent prognostic factor for seizure-free outcome after epilepsy surgery in MR+ cases. Several groups reported comparably favourable outcomes in non-lesional cases after delineation of the epileptogenic zone by invasive recordings with consecutive complete resection (Paolicchi *et al*., 2000; Siegel *et al*., 2001; Blume *et al*., 2004; Alarcón *et al*., 2006; Bien *et al*., 2009; Krsek *et al*., 2009; Dorward *et al*., 2011). However, this potential correlation was not analysed or reported in detail for the majority of studies regarding outcome in MRI-negative epilepsy surgery. In addition, the selection of candidates for invasive recordings, interpretation and weighting of iEEG findings, and application of variable non-invasive diagnostic tools differ markedly between centres. Thus, a general conclusion of whether or not outcome levels of patients with MR+ epilepsies can be achieved in MRI-negative cases cannot be drawn.

Subgroup of focal cortical dysplasia

FCD is the most common histopathological finding in children surgically treated for epilepsy (Harvey *et al*., 2008). Up to 25% of pathologically confirmed FCD in adults remains MR- (Widdess-Walsh *et al*., 2006). Data from studies comparing post-operative outcomes in MR+ and MRI-negative FCD are inconclusive. Some studies reported a significantly worse outcome in MRI-negative cases (Siegel *et al*., 2001; Cossu *et al*., 2008; Phi *et al*., 2010), while others reported no difference (Hader *et al*., 2004; Park *et al*., 2006; Siegel *et al*., 2006; Widdess-Walsh *et al*., 2007; Krsek *et al*., 2009).

Park *et al*. (2006) studied 30 children, aged 1.5 to 18.3 years, with FCD. Six patients had dual pathology, with a tumour and FCD. Engel class I was achieved in 67% of children. Six of 8 MRI-negative patients had a favourable outcome (Engel class I and II), similar to MR+ patients. Krsek *et al*. (2009) investigated 144 children and adolescents (<20 years) and 5 young adults (20-25 years) who received surgery at the Miami Children's Hospital. Presurgical MRI (108 with 1.5T and 41 with 0.5T) was re-evaluated. The MRI was negative in 26 patients. One hundred patients, including all MRI-negative children, underwent iEEG. Seizure outcome did not differ between patients who were MRI-negative (54% Engel class I) and MR+ (55% Engel class I). In contrast to these studies, Phi *et al*. (2010) in Seoul reported a significant difference in univariate analysis regarding seizure outcome between MRI-negative and MR+ histopathologically-proven FCD. Of 41 children with FCD, 49% became seizure-free

Table 1. Seizure outcomes in MR- patients.

Authors	Year of publication	Cohort	Aim of study	N	Period of recruitment	Follow-up (years)	Seizure-free outcome (%)	Outcome: Engel class I (%)	Outcome: Other (%)
Téllez-Zenteno *et al.*	2010	C+A	Meta-analysis for comparing MR+ and MR-	398	1995-2007	≥1	43		
		C		93			45		
Bell *et al.*	2009	C+A	Outcome MR- TLE	40	1997-2005	≥1	60		
Bien *et al.*	2009	C+A	Outcome MR+ and MR-	29	2000-2006	≥0.5	38	45	
Chapman *et al.*	2005	C+A	Outcome MR-	24	1994-2001	≥1	37	45	
Cukiert *et al.*	2001	C+A	Outcome and iEEG in MR-/diffuse MRI	10	1997-2000	≥1	90		
Dorward *et al.*	2011	C	Outcome in MR- ETLE	22	1994-2007	≥2		36	
Jayakar *et al.*	2008	C+(A)	Outcome MR-	102	?	≥2	44		
Krsek *et al.*	2009	C+(A)	FCD study	26	1986-2006	≥2		54	
Lee *et al.*	2005	C+A	Outcome MR-	89	1995-2002	≥2	47		
McGonigal *et al.*	2007	C+A	iEEG	20	2000-2006	1	55		
Park *et al.*	2002	C+A	iEEG	18	1995-2000	≥1			44 (>90% seizure reduction)
RamachandranNair *et al.*	2007	C	Functional imaging	22	1998-2005	≥0.75	36		77 (<Engel IIIa)
Schneider *et al.*	2012	C+A	Functional imaging	18	2008-2010	≥2	56		
Seo *et al.*	2011	C	Functional imaging	25	2006-2009	≥1	48		
Siegel *et al.*	2001	A	MR- outcome	24	1992-1999	≥2		83	
Thivard *et al.*	2011	A	(Functional) imaging	12	2003-2006	NR		67	
Wetjen *et al.*	2009	C+A	iEEG and MR- outcome	28	1992-2002	>1	36	50	
Wu *et al.*	2013	A	Functional imaging	18	1990-2009	≥1	22		55 (Engel I+II)
Zhang *et al.*	2011	C+A	Functional imaging	20	2006-2009	≥1	35		

N: number of patients; C: children; A: adults; (A): young adults; iEEG: invasive long-term EEG recording; NR: not reported.

one year after surgery and 33% remained seizure-free after five years. The precise rate of seizure freedom in 19 MRI-negative children was not specified in the text.

How can outcome be predicted and potentially improved?

In the subgroup of MRI-negative patients with histopathological substrate, advances in structural MRI are crucial for improving outcome. However, cases with negative pathology represent a different entity of epilepsy and an improvement of only structural imaging will most likely not influence outcome (Bien *et al*., 2009). The underlying pathophysiological mechanisms may be related to disturbed network connections and functions acting on a submicroscopic level. There is hope that multimodal functional imaging may improve the selection of patients and postsurgical outcome for MRI-negative patients both with and without lesion based on histopathology. Different methods have been studied and most reported studies were observational and monocentric, leading to a bias in recruitment of patients. The outcome of surgery may be better when only patients with positive results of a specific diagnostic method are included.

Higher rates of seizure freedom have been demonstrated in patients with unifocal clusters of interictal MEG dipoles and complete resection of the identified zone, compared to multifocal or widespread activity and/or incomplete resection (RamachandranNair *et al*., 2007; Zhang *et al*., 2011; Schneider *et al*., 2012; Wu *et al*., 2013). Electrical source imaging (ESI) in EEG from dense array surface electrodes was applied in 10 MRI-negative patients (Brodbeck *et al*., 2010). Resection covered the interictal spike zone, identified by ESI, in 8 patients and the outcome was favourable in all of them. The other two patients had Engel class I and Engel class IV outcome.

Fluoro-2-desoxy-D-glucose positron emission tomography (FDG-PET) may contribute crucial information in young children with severe epileptic encephalopathies (Chugani *et al*., 1993). Resection of hypometabolic areas revealed by FDG-PET may (Lee *et al*., 2005) or may not (Dorward *et al*., 2011) correlate with a better outcome in MRI-negative cases.

Ictal single-photon emission computed tomography (SPECT), and particularly subtracted ictal-interictal SPECT (SISCOM) (co-registered with MRI), may add substantial information in MRI-negative cases. High concordance of areas with ictal hyperperfusion and the epileptogenic zone, as defined by iEEG, has been demonstrated (Seo *et al*., 2011). A higher rate of seizure freedom in cases with complete resection of the areas of hyperperfusion has been described (Bell *et al*., 2009). Discordance of SISCOM results was related to poor outcomes in MRI-negative patients (Bien *et al*., 2009). However, some studies did not find any correlation between SPECT results and outcome (Chapman *et al*., 2005; Lee *et al*., 2005; Jayakar *et al*., 2008).

The vast majority of patients with MRI-negative epilepsy should be investigated by invasive recordings before a final decision for and tailoring of resection is possible. Complete resection of the seizure-onset zone, as defined by invasive recordings, leads to higher seizure freedom rates (Blume *et al*., 2004; RamachandranNair *et al*., 2007; Wetjen *et al*., 2009; Schneider *et al*., 2012). There is some evidence that resection of seizure zones, presenting with high-amplitude, frequent oscillations at onset, may be associated with better outcome, compared to other types of ictal activity (Park *et al*., 2002; Wetjen *et al*., 2009). In patients with frontal lobe epilepsies, success rates in localising seizure onset by stereo-EEG were identical in MRI-negative and MR+ cases (McGonigal *et al*., 2007).

The necessity for iEEG in some patients may be avoided by establishing convergent results from several non-invasive functional studies using a multimodal approach (Jayakar *et al*., 2008). In the study of Jayakar *et al*. (2008), 20/102 children underwent resective surgery for MRI-negative epilepsy without invasive recordings. The outcome also correlated with the presence of focal interictal spike discharges on scalp EEG, corresponding to the resected area. Whereas SPECT did not correlate with outcome, a favourable outcome was more frequent in cases with complete resection of the epileptogenic zone, as defined by the combination of SPECT and focal interictal spikes. Bien *et al*. (2009) analysed the value of semiology, interictal and ictal surface EEG, PET, SPECT, SISCOM, and MRI post-processing in MR-patients. Post-processing and semiology rarely provided information on localisation, however, when this was provided, positive and negative predictive values were high. Concordant information based on semiology, interictal surface EEG, and MRI post-processing was predictive of good outcome, whereas discordance between semiology, interictal surface EEG, MRI post-processing, and SISCOM was predictive of poor seizure outcome. Seo *et al*. (2011) scored the concordance of MEG, PET, and SISCOM with iEEG in MRI-negative children and reported a tendency towards better outcomes in patients with higher cumulative scores. A combination of lack of contralateral interictal spikes with complete resection of the SISCOM-identified zone of hyperperfusion and non-specific MRI findings correlated with a high rate of seizure freedom in patients with MRI-negative temporal lobe epilepsies (Bell *et al*., 2009). Thivard *et al*. (2011) compared the sensitivity and specificity of PET (visual and statistical analysis), DTI, and voxel-based morphometry in 20 MR- patients. The greatest sensi-

tivity was demonstrated for unblinded, visual analysis of PET. However, DTI was superior with regards to ETLE and exhibited the overall greatest specificity. A combination of PET and DTI resulted in an increase of sensitivity in mesial temporal lobe epilepsy and frontal lobe epilepsy, but not in lateral temporal lobe epilepsy.

The diagnostic value of each non-invasive method and the optimal combination in multimodal work-up remain unclear. It should be noted that the use of concordant results of two or more repeated presurgical investigations may be a beneficial approach in order to select appropriate candidates for surgery, and may help to avoid invasive procedures in unpromising cases (Lee *et al*., 2005; Jayakar *et al*., 2008).

What are the risks of surgery in cases with normal pathology?

Resection of a pathologically-proven lesion is not associated with a higher risk of neurocognitive impairment following surgery for either MRI-negative or MR+ focal epilepsies. However, normal histopathology is reported in one to two thirds of specimens. Helmstaedter *et al*. (2011) hypothesized that temporal lobe resections in MRI-negative adults with normal histopathology may result in a more severe loss of memory function, compared to lesional cases, and compared 15 MRI-negative patients with normal pathology to 15 matched controls (MR+, positive histopathology). While pre-operative memory functions were significantly better in patients with normal histopathology, these patients experienced a marked decrease in function after resection. Post-operative performance was comparably low in both groups. The authors concluded that surgery should be considered with caution in temporal lobe epilepsy patients with normal MRI and normal memory function.

There is no comparable reported study in children. Dorward *et al*. (2011) analysed seizure and neurocognitive outcome in 33 patients after surgery for MR-ETLE. Pre- and post-operative neuropsychological assessments were conducted in 23 children. Intellectual functioning measured by full-scale IQ was stable. Children with left-sided resection demonstrated significant improvements in performance IQ and performance of a measure for non-verbal reasoning. Other tested domains remained unchanged. A shortcoming is the inclusion of patients with different kinds of surgical procedures, among which include a considerable number of multiple subpial transections (MST), with or without resection. The potential differences between 14 children with normal pathology and 18 with a histopathological substrate were not tested.

Conservative treatment of MRI-negative focal epilepsy

Wirrell *et al*. (2011) reported the long-term outcome of childhood-onset focal epilepsies. Between 1980 and 2004, 359 patients were newly diagnosed with epilepsy at Rochester, Minnesota. After reviewing all available clinical data, 215 (60%) were classified as non-idiopathic focal epilepsies. A follow-up of at least one year (mean: 134 months) was documented in 206 patients. A seizure-free period of at least 12 months, before the end of the follow-up, was noticed in 81%. This rate was significantly higher, compared to the symptomatic group of 95 patients (55%). MRI was negative in 78 patients, of whom 77% became seizure-free. Other studies were conducted in the pre-MRI era. Camfield and Camfield (2002) investigated a group of 132 children with normal CT, intelligence, and neurological examinations. Two thirds of the patients became seizure-free after a mean follow-up of 88 months. Sillanpaa *et al*. (1998) revealed a seizure freedom rate of 63% in 32 children with cryptogenic focal epilepsy. Shinnar *et al*. (1999) reported that, of 34 children with cryptogenic focal epilepsy, 82% were seizure-free after a mean follow-up of 8.3 years.

In adults, aetiology of focal epilepsies was shown by Semah *et al*. (1998) to be a major prognostic factor. In this hospital-based study from Paris, a total of 2,200 adult outpatients were included in an observational survey. Partial epilepsies were diagnosed in 62%. Seizure control (for more than one year) was achieved in 45% of 408 patients with cryptogenic focal epilepsies, compared to 35% of 535 with symptomatic aetiology. However, seizure control required polytherapy for the majority of patients.

These rates of seizure control in cryptogenic focal epilepsies markedly differ from reported outcomes following epilepsy surgery in MRI-negative patients, although the quality of applied imaging is largely comparable. Importantly, only patients with drug resistance enter presurgical programs and thus represent a difficult-to-treat subset of patients with cryptogenic epilepsies. To date, there is only one reported study in which seizure outcome was compared between MRI-negative patients who received surgery and those who were conservatively treated, all of whom underwent presurgical work-up (Bien *et al*., 2009). In the years 2000-2006, a total number of 1,192 patients (children over 0.5 years and adults) underwent presurgical evaluation at the Epilepsy Center in Bonn. A clear MRI lesion was found in 1,002 patients and surgery was performed for 736 patients. From the MRI-negative group, 29 of 190 patients underwent surgery. Conservative treatment led to a significantly lower rate of seizure freedom in MRI-negative cases (19/120 [16%] with documented follow-up), compared to surgically treated

MRI-negative patients (38%). The response to antiepileptic drugs was comparable to conservatively treated MR+ patients (22/142 [15%] with documented follow-up).
Despite the difficulties in diagnostic work-up and the significant number of evaluations that do not result in surgery, these results clearly demonstrate the value of epilepsy surgery in this challenging population.

Conclusion

Epilepsy surgery should be considered in children with pharmaco-refractory, non-idiopathic focal epilepsies even in the absence of a potentially epileptogenic lesion based on structural MRI. It would appear that epilepsy surgery is superior to further antiepileptic treatment in this challenging group of patients with pharmaco-resistant epilepsy. □

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